Obesità: un fattore di rischio per la salute del cervello

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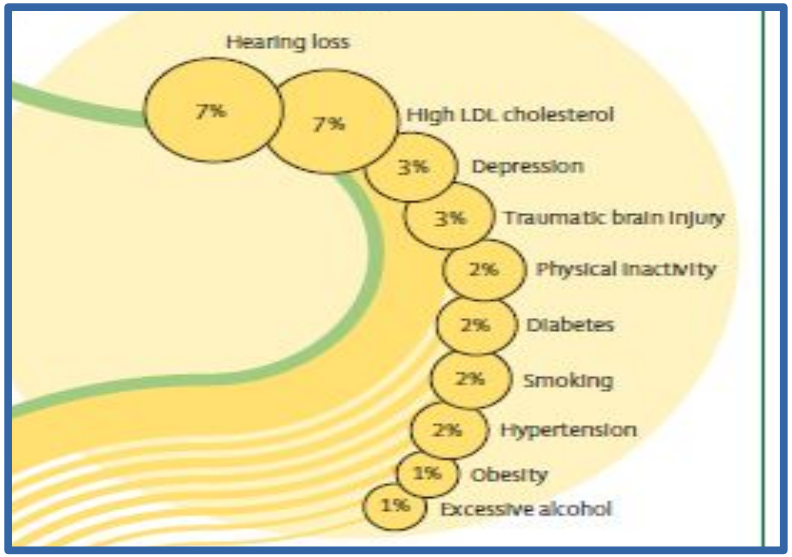
CREMONA SOLIDALE
AZIENDA SPECIALE COMUNALE PER I SERVIZI ALLA PERSONA

Outline

- **Epidemiologia**
- **Quali interventi per il controllo dell’obesità?**
- **Obesità e decadimento cognitivo**

Dementia prevention, intervention, and care: 2024 report of the *Lancet* standing Commission

Gill Livingston, Jonathan Huntley, Kathy Y Liu, Sergi G Costafreda, Geir Selbæk, Suvarna Alladi, David Ames, Sube Banerjee, Alistair Burns, Carol Brayne, Nick C Fox, Cleusa P Ferri, Laura N Gitlin, Robert Howard, Helen C Kales, Mika Kivimäki, Eric B Larson, Noeline Nakasujja, Kenneth Rockwood, Quincy Samus, Kokoro Shirai, Archana Singh-Manoux, Lon S Schneider, Sebastian Walsh, Yao Yao, Andrew Sommerlad, Naaheed Mukadam**



www.thelancet.com Published online July 31, 2024 https://doi.org/10.1016/S0140-6736(24)01296-0

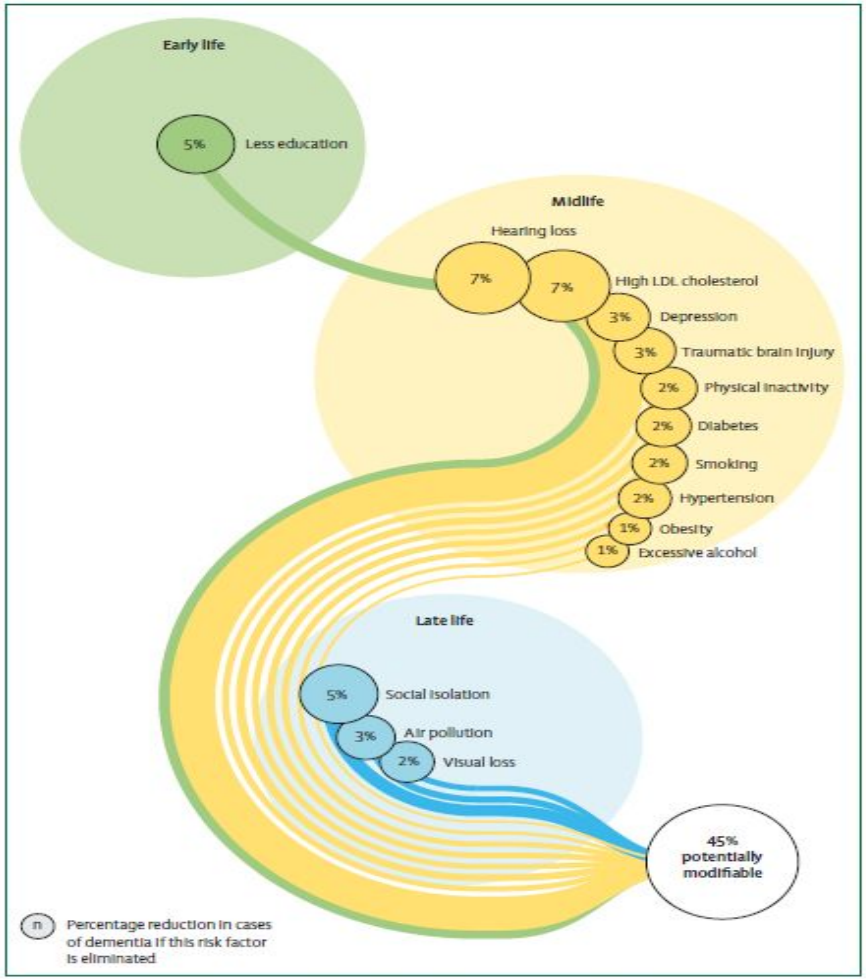
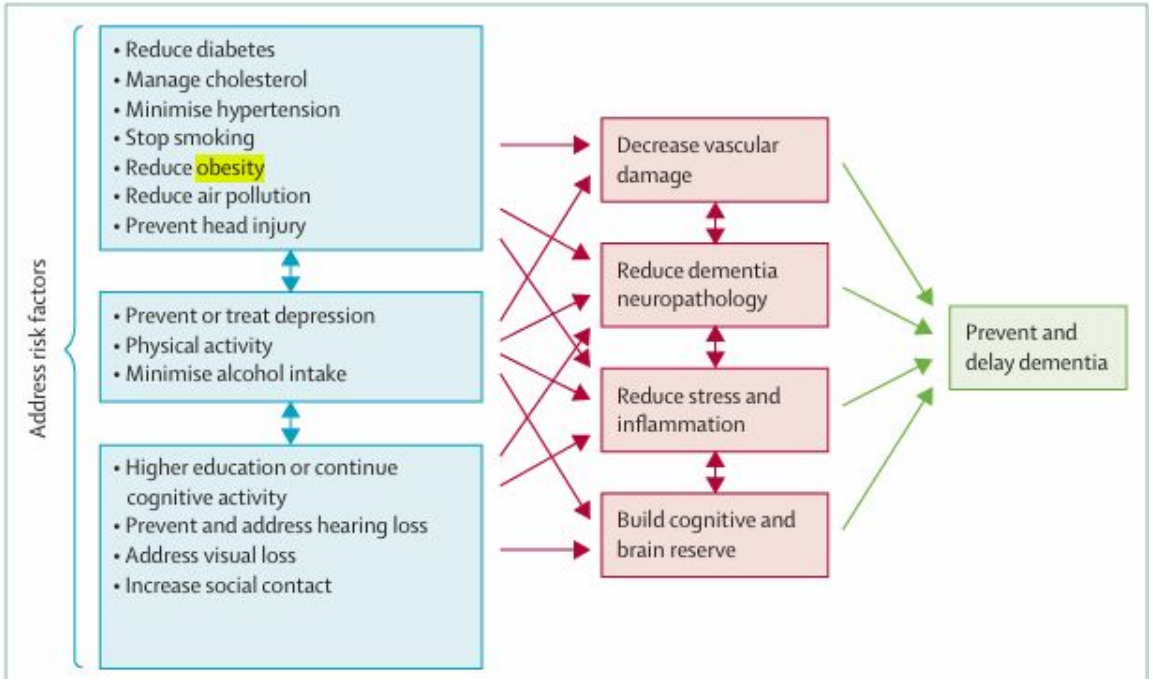


Figure 9: **Population attributable fraction of potentially modifiable risk factors for dementia**

Possible brain mechanisms for enhancing or maintaining cognitive reserve and risk reduction of potentially modifiable risk factors in dementia



www.thelancet.com Published online July 31, 2024 https://doi.org/10.1016/S0140-6736(24)01296-0

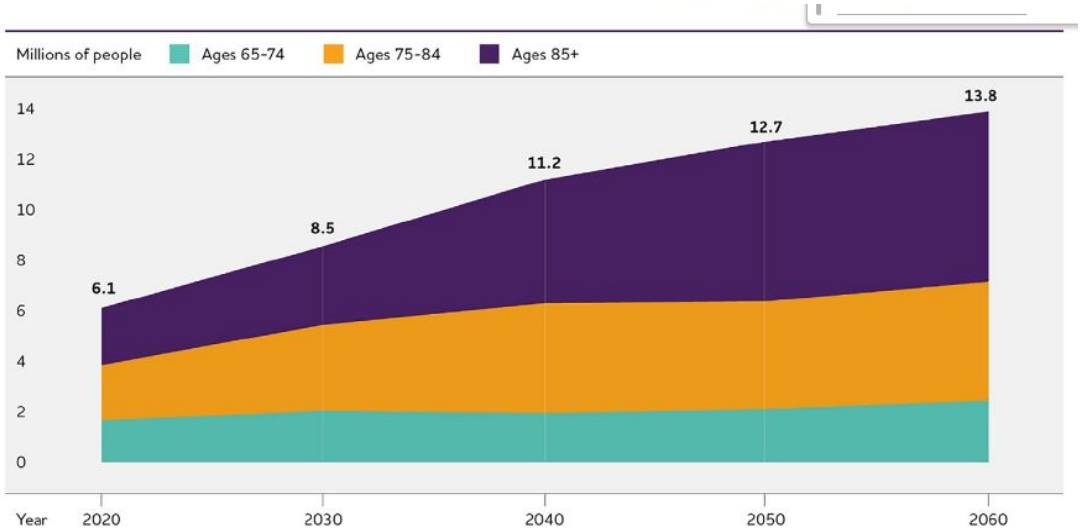
Prevalenza della demenza

50 million people worldwide living with dementia in 2020.

82 million in 2030

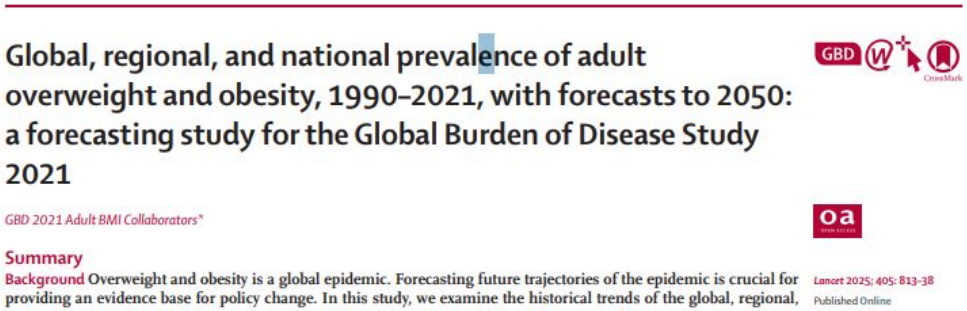
152 million in 2050.

USA



Alzheimer Disease Int 2024

***Alzheimer's Dement.* 2024;20:3708–3821**



Global, regional, and national prevalence of adult overweight and obesity, 1990–2021, with forecasts to 2050: a forecasting study for the Global Burden of Disease Study 2021

GBD 2021 Adult BMI Collaborators*

Summary

Background Overweight and obesity is a global epidemic. Forecasting future trajectories of the epidemic is crucial for providing an evidence base for policy change. In this study, we examine the historical trends of the global, regional,

Lancet 2025; 405: 813-38
Published Online

- In **2021**, an estimated **1·00 billion adult males** and **1·11 billion adult females** had **overweight and obesity**
- China (402 million individuals), followed by India (180 million) and the USA (172 million)
- **By 2050**, we forecast that the total number of adults living with **overweight and obesity will reach 3·80 billion**, over half of the likely global adult population at that time

Prevalenza dell'obesità

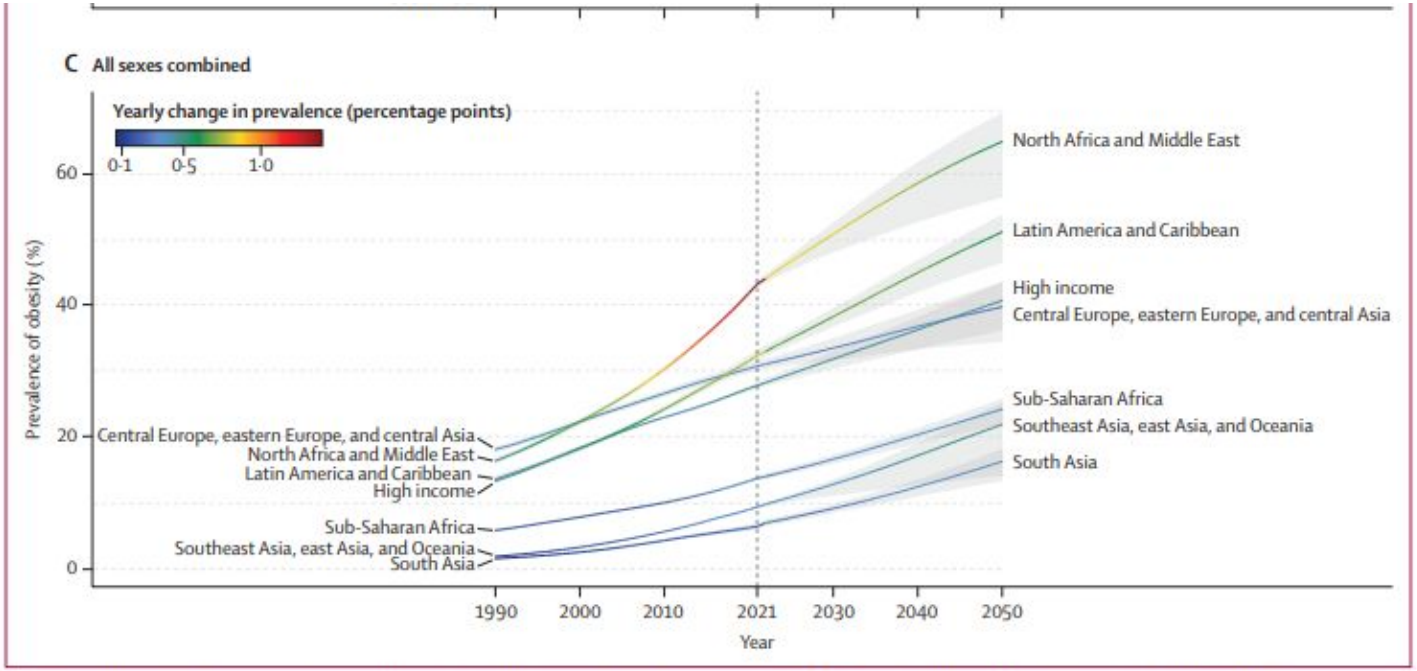
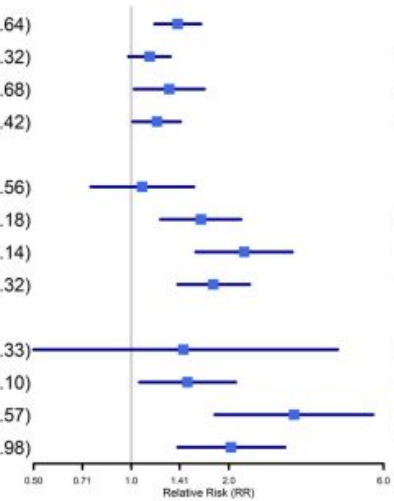


Figure 4: **Estimated age-standardised prevalence of obesity in adults aged 25 years and older by sex, globally and by super-region, 1990–2050**
(A) Females. (B) Males. (C) All sexes combined. Shaded regions are 95% uncertainty intervals.

Lancet 2025; 405: 813–38
Published Online

Obesità e deficit cognitivo-demenza (midlife)

Group	Included studies	Sample size	RR (95%CI)	I^2 (%)	P-Value
Cognitive impairment and dementia					
Underweight	9	58361	1.39 (1.18-1.64)	0	0.44
Overweight	11	64265	1.14 (0.98-1.32)	77	<0.01
Obesity	11	64265	1.31 (1.02-1.68)	84	<0.01
High BMI	13	67753	1.20 (1.01-1.42)	89	<0.01
AD					
Underweight	4	22253	1.08 (0.75-1.56)	0	0.62
Overweight	5	24253	1.64 (1.23-2.18)	67	0.01
Obesity	5	24253	2.23 (1.58-3.14)	51	0.07
High BMI	6	27721	1.79 (1.39-2.32)	75	<0.01
VaD					
Underweight	3	13719	1.47 (0.50-4.33)	65	0.06
Overweight	4	22253	1.49 (1.06-2.10)	51	0.08
Obesity	4	22253	3.18 (1.81-5.57)	68	0.01
High BMI	5	25721	2.03 (1.39-2.98)	77	<0.01



Qu Y et al Neurosci Biobehav Rev . 2020 Aug:115:189-198.

Outline

- **Epidemiologia**
- **Quali interventi per il controllo dell’obesità?**
- **Obesità e decadimento cognitivo**

Weight loss is associated with improvements in cognitive function among overweight and obese people: A systematic review and meta-analysis

Nicola Veronese[a,b,*,1], Silvia Facchini[a,1], Brendon Stubbs[c,d,e,1], Claudio Luchini[f,g], Marco Solmi[b,h], Enzo Manzato[a,i], Giuseppe Sergi[a], Stefania Maggi[i], Theodore Cosco[j], Luigi Fontana[k,l,m]

Weight loss was associated with a significant improvement in attention and memory in both longitudinal studies and RCTs
Executive function and language improved in longitudinal and RCT studies, respectively

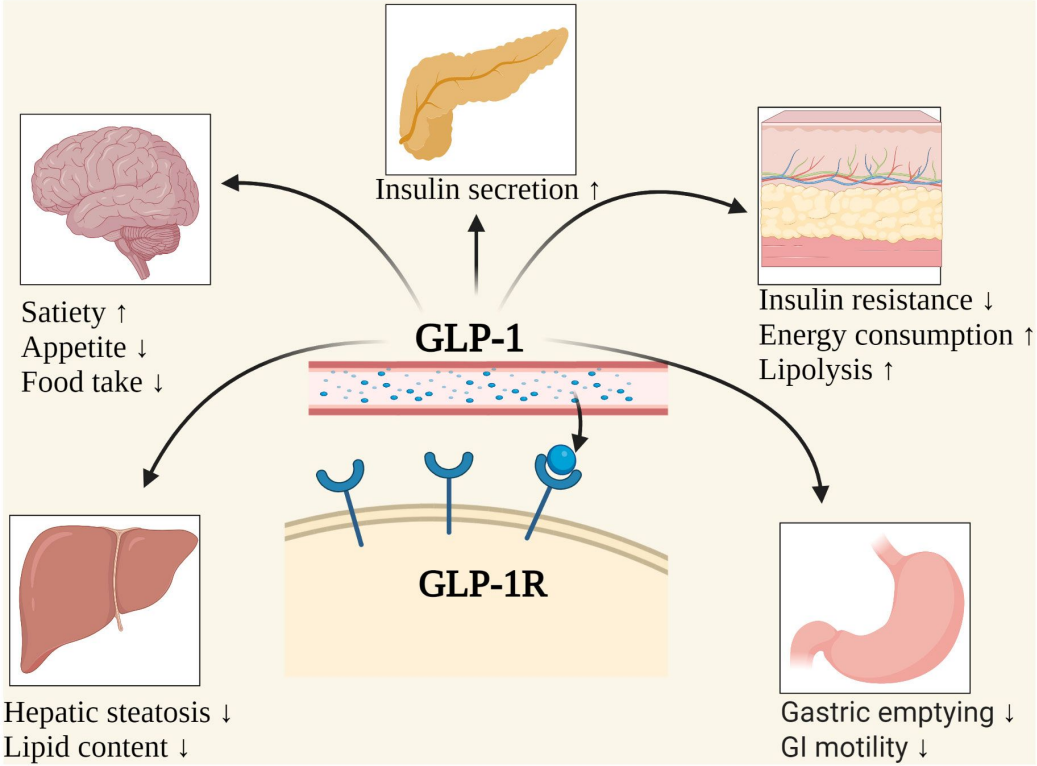
Neuroscience and Biobehavioral Reviews 72 (2017) 87–94

Terapia farmacologica per l'obesità: agonisti GLP-1

	Naltrexone plus Bupropion	Phentermine plus topiramate extended release	Orlistat	Liraglutide 3 mg	Semaglutide 2·4 mg	Tirzepatide
Dosage form and dosing	8 mg naltrexone–90 mg bupropion; starting at one tablet daily; increasing by one tablet daily once per week over 4 weeks to maximum two tablets twice daily	3·75 mg phentermine–23 mg topiramate once daily, oral for 14 days; then 7·5/46 mg; after 12 weeks when <3% weight loss, can increase to 15/92 mg	60–120 mg three times a day, with meals, oral	Starting at 0·6 mg daily, subcutaneous; increasing every week: 1·2 mg, 1·8 mg, 2·4 mg, and 3·0 mg (maximum)	Starting at 0·25 mg weekly, subcutaneous; increasing every 4 weeks: 0·5 mg, 1·0 mg, 1·7 mg, and 2·4 mg (maximum)	Starting at 2·5 mg weekly, subcutaneous; increasing by 2·5 mg weekly after at least 4 weeks; maintenance 5, 10, or 15 mg weekly
Mechanism of action for weight reduction	Dopamine and noradrenaline reuptake inhibitor (bupropion); opioid receptor antagonist (naltrexone)	Sympathomimetic (phentermine); GABA receptor activation, and carbonic anhydrase inhibition (topiramate)	Inhibition of gastric and pancreatic lipase	GLP-1 receptor agonism in appetite and reward centres; slowing gastrointestinal transit	GLP-1 receptor agonism in appetite and reward centres; slowing gastrointestinal transit	Dual GIP/GLP-1 receptor agonism
Contraindications	Chronic opioid use, acute	Glaucoma,	Chronic malabsorption	Personal or family	Personal or family history	Personal or family history

Lingvay I et al Lancet 2024

Agonisti GLP-1: meccanismo di azione



Wang JY, et al. Front Endocrinol (Lausanne). 2023.

Outline

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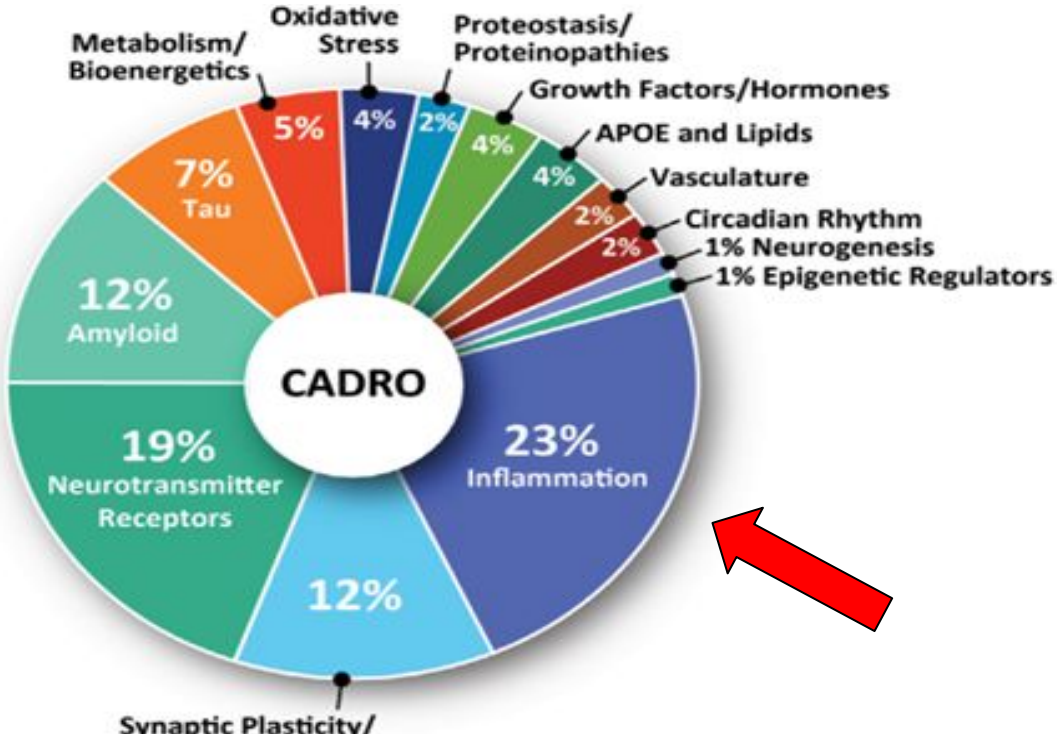
- **Quali interventi per il controllo dell’obesità?**
- **Obesità e decadimento cognitivo**

DOI: 10.1002/trc2.12465

REVIEW ARTICLE

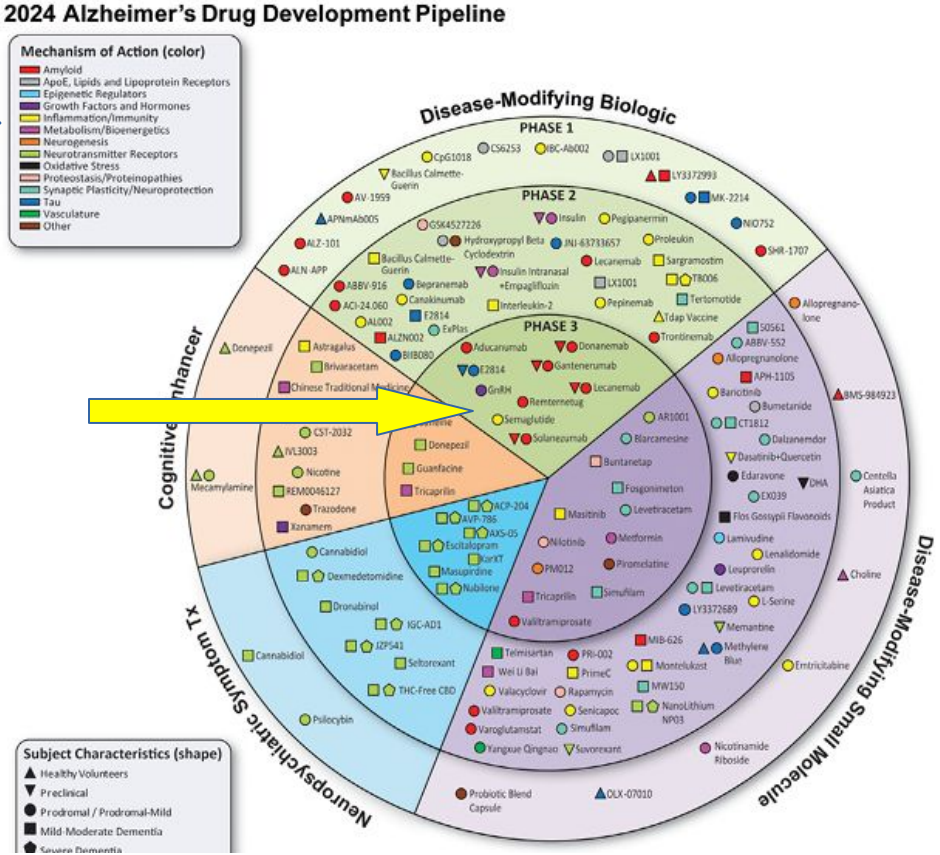
Alzheimer's & Dementia
Translational Research & Clinical Interventions

Alzheimer's disease drug development pipeline: 2024



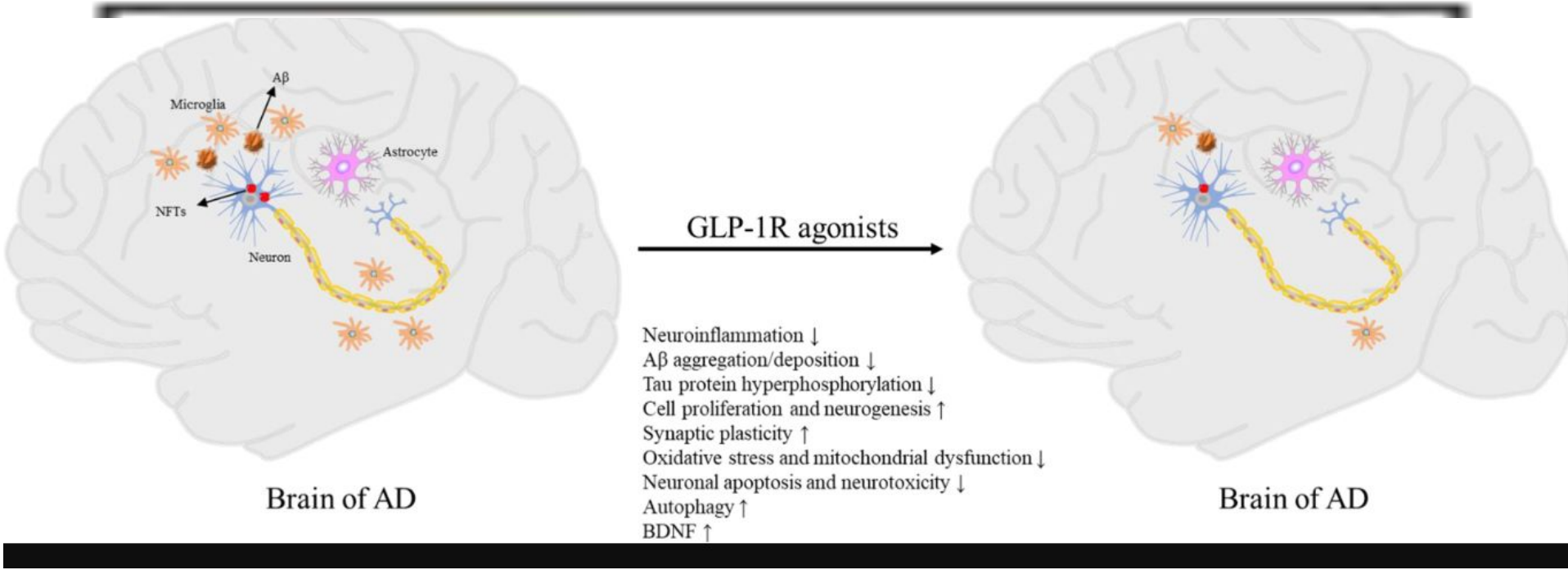
Cummings J et al, Alzheimer's Dementia 2024

Inflammation-immunity



Cummings J et al, Alzheimer's Dementia 2024

Meccanismo di azione dei GLP-1 agonisti e demenza

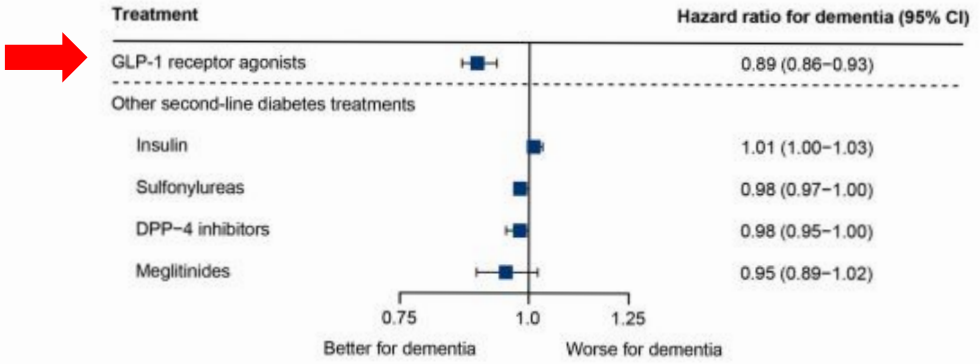


Du H, et al. Front Endocrinol (Lausanne). 2022.

Treatment with glucagon-like peptide-1 receptor agonists and incidence of dementia: Data from pooled double-blind randomized controlled trials and nationwide disease and prescription registers

Caroline Holm Nørgaard[1,2] | Sarah Friedrich[3] | Charlotte Thim Hansen[4] | Thomas Gerds[5] | Clive Ballard[6] | Daniel Vega Møller[4] | Lotte Bjerre Knudsen[7] | Kajsa Kvist[4] | Bernard Zinman[8] | Ellen Holm[9] | Christian Torp-Pedersen[1,10] | Lina Steinrud Mørch[4]

patients randomized to placebo developed dementia. GLP-1 RA, glucagon-like peptide-1 receptor agonist; RCT, randomized controlled trial

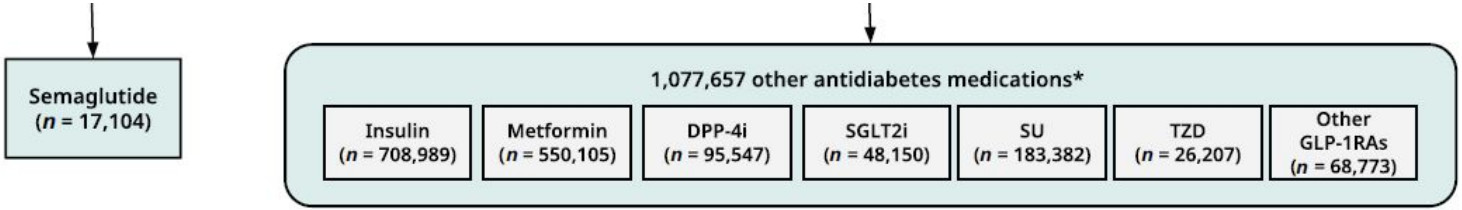


Alzheimer's Dement. 2022;8:e12268

Associations of semaglutide with first-time diagnosis of Alzheimer's disease in patients with type 2 diabetes: Target trial emulation using nationwide real-world data in the US

William Wang[1] | QuangQiu Wang[2] | Xin Qi[3] | Mark Gurney[2] | George Perry[2,4] | Nora D. Volkow[5] | Pamela B. Davis[6] | David C. Kaelber[7] | Rong Xu[2]

Patients had at least one condition for semaglutide prescription (obesity, hypertension, hypercholesterolemia, heart diseases, stroke, or A1C ≥8.5%)

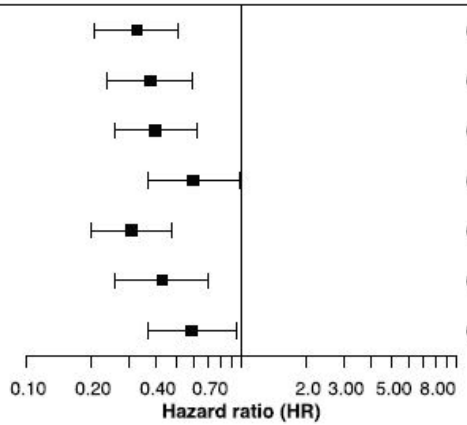


Alzheimer's Dement. 2024;1–12.

(A)

Risk of first–time diagnosis of Alzheimer's disease in patients with type 2 diabetes (comparison between matched semaglutide vs other antidiabetes medications groups)

Size/Group	Exposure group	Comparison group	Exposure Group Cases (overall risk)	Comparison Group Cases (overall risk)	HR (95% CI)
17,087	Semaglutide	Insulin	27 (0.16%)	73 (0.43%)	0.33 (0.21 to 0.51)
17,080	Semaglutide	Metformin	27 (0.16%)	68 (0.40%)	0.38 (0.24 to 0.59)
15,878	Semaglutide	DPP–4i	27 (0.17%)	62 (0.39%)	0.40 (0.26 to 0.63)
15,288	Semaglutide	SGLT2i	26 (0.17%)	40 (0.26%)	0.60 (0.37 to 0.98)
16,503	Semaglutide	SU	27 (0.16%)	80 (0.49%)	0.31 (0.20 to 0.48)
10,847	Semaglutide	TZD	24 (0.22%)	51 (0.47%)	0.43 (0.26 to 0.70)
17,029	Semaglutide	Other GLP–1RAs	27 (0.16%)	44 (0.26%)	0.59 (0.37 to 0.95)



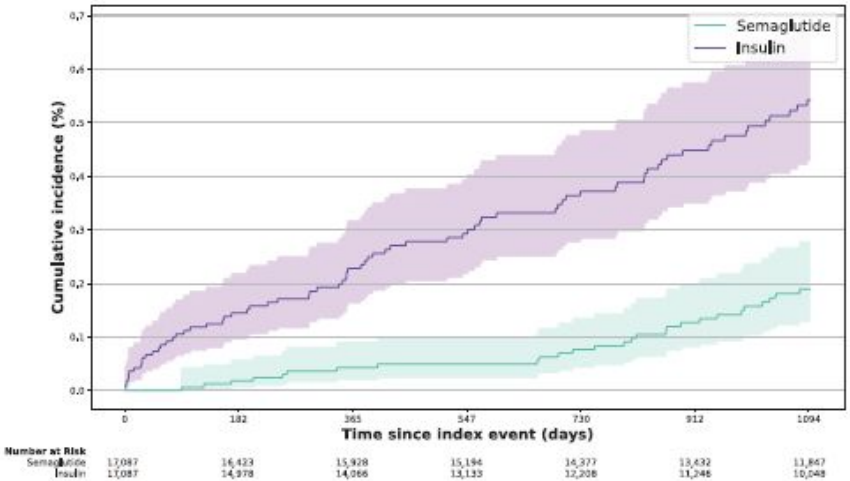
(B)

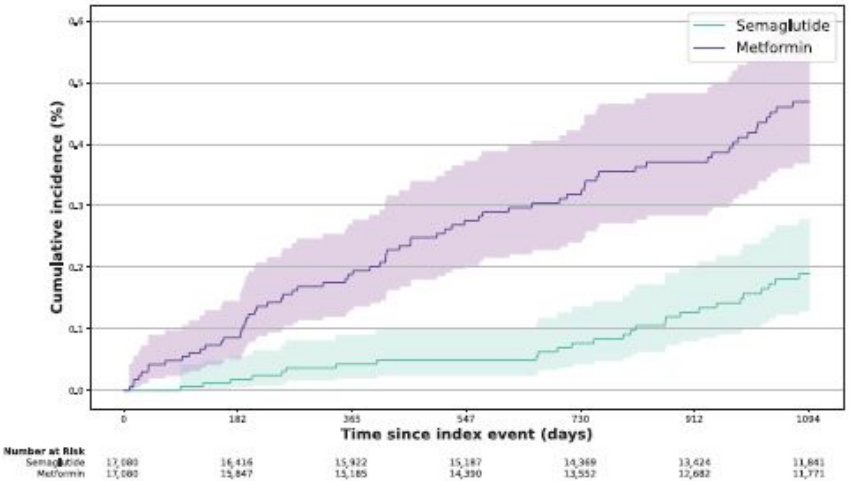
These results were similar for older patients, both genders, and those with and without obesity.

40% to 70% decrease in first-time AD diagnoses

Alzheimer's Dement. 2024;1–12.

Riduzione dell’incidenza e progressione nel tempo





Alzheimer’s Dement. 2024;1–12.

Original Investigation | Diabetes and Endocrinology

Neurodegeneration and Stroke After Semaglutide and Tirzepatide in Patients With Diabetes and Obesity

Huan-Tang Lin, MD, PhD; Yung-Fong Tsai, MD, PhD; Pei-Lun Liao, MSc; James Cheng-Chung Wei, MD, PhD

During a 7-year follow-up, GLP-1RA users had lower risk of:

- **Dementia (HR, 0.63; 95%CI, 0.50-0.81)**
- **Stroke (HR, 0.81; 95%CI, 0.70-0.93)**
- **All-cause mortality (HR, 0.70; 95%CI, 0.63-0.78)**

JAMA Network Open. 2025;8(7):e2521016.

Quale il futuro?

Cummings *et al. Alzheimer's Research & Therapy* (2025) 17:14
https://doi.org/10.1186/s13195-024-01666-7

Alzheimer's Research & Therapy

RESEARCH Open Access

evoke and evoke+: design of two large-scale, double-blind, placebo-controlled, phase 3 studies evaluating efficacy, safety, and tolerability of semaglutide in early-stage symptomatic Alzheimer's disease

Jeffrey L. Cummings[1,15*], Alireza Atri[2,3,4], Howard H. Feldman[5], Oskar Hansson[6,7], Mary Sano[8], Filip K. Knop[9,10,11,12], Peter Johannsen[12], Teresa León[12] and Philip Scheltens[13,14]

Conclusioni

- **Incremento epidemiogico demenza ed obesità**
- **Necessità di ottimizzare il controllo dei fattori di Rischio**
- **Il ruolo emergente degli agonisti GLP-1 nella prevenzione della demenza**
- **Necessità di definire il ruolo degli agonisti GLP-1 nelle fasi precoci della malattia di Alzheimer**

Agonisti GLP-1: quali?

Table 1. Comparison of GLP-1RAs used in type 2 diabetes mellitus

Date	Brand name	GLP-1RA	Half-life	Dose (SC)	Molecular formula	Clinial trial focus
2005	Byetta	Exenatide	2.4 h	5 μg or 10 μg b.i.d sc	$C_{149}H_{234}N_{40}O_{47}S$	Parkinson disease
2010	Victoza/Saxenda	Liraglutide	11-13 h	0.6 mg and 1.2 or 1.8 mg q.d sc	$C_{172}H_{265}N_{43}O_{51}$	Cardiovascular disease
2013	Adlyxin (U.S)/Lyxumia (EU)	Lixisenatide	2–4 h	10 μg then 20 μg q.d sc	$C_{215}H_{347}N_{61}O_{65}S$	Early Parkinson disease
2014	Tanzeum	Albiglutide	6-8 h	30 or 50 mg q.w sc	$C_{148}H_{224}N_{40}O_{45}$	Cardiovascular disease
2014	Trulicity	Dulaglutide	108-112 h	0.75 or 1.5 mg q.w sc	$C_{2646}H_{4044}N_{704}O_{836}S_{18}$	Type 2 diabetes
2017	BYDUREON BCise	Exenatide (ER)	2 w	2 mg q.w sc	$C_{184}H_{282}N_{50}O_{60}S$	Type 1 diabetes
2017	Ozempic	Semaglutide	6-7 d	0.25 mg then 0.5 mg q.w sc	$C_{187}H_{291}N_{45}O_{59}$	obesity-related heart failure
2019	Rybelsus	Oral Semaglutide	24 h	3 mg then 7 mg q.d po	$C_{187}H_{291}N_{45}O_{59}$	Type 2 diabetes

Form: Pen, SC injection; po, orally
q.d once daily, *q.w* once weekly, *b.i.d* twice daily, *t.i.d* three times daily, *SC* subcutaneous administration, *w* week, *po* orally
Date: Refers to the date when the drug was approved by the U.S. Food and Drug Administration (FDA)
Clinical Trial Focus: Describes the main diseases targeted in recent clinical trials

Zheng Z et al Signal Transduction and Targeted Therapy (2024) 9:234

Agonisti GLP-1: quali differenze?

Table 2. Comparative overview of efficacy and adverse effects of mainstream GLP-1RA medications

	CV benefit	Renal benefit	Weight loss	Patient adherence	HbA1c reduction	HbA1c problem	Injection reactions	GI side effects	Antibody issues
Exenatide					+	−−	−−	−	−−
Lixisenatide					+	−−	−−	−	−
Oral Semaglutide	++				+	−−		−−	
Dulaglutide	++	+		++	++	−−−			
Liraglutide		+	++	++	++	−−		−−	
Exenatide (ER)				++	++	−			−
Semaglutide (S.C)	+++	+++	+++	++	++			−	

CV cardiovascular, *GI* gastrointestinal, *RE* extended-release, *SC* subcutaneous administration
The "+" and "−" symbols indicate the efficacy profile or adverse effect profile of each parameter, with more symbols meaning greater strength or severity. More "+" signs indicate a greater benefit. More "−" signs indicate more severe side effect issues

Zheng Z et al Signal Transduction and Targeted Therapy (2024) 9:234